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Comparing ecstasy users and non-users in a population-based and co-twin control design across multiple traits

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HIGHLIGHTS

- Ecstasy users differ from non-users on several characteristics.
- Ecstasy use often precedes first use of other illicit substances.
- Ecstasy use (or related environmental factors) may increase risk of substance use.

ABSTRACT

Objective: Ecstasy is one of the most commonly used illicit substances in Western countries. The aim of this study is to identify characteristics of ecstasy users in a large population-based sample of adults aged 18–45 years.
Method: With generalized estimating equation models we explored the association between self-reported lifetime ecstasy use and urbanicity, educational attainment, health, wellbeing, stress, other substance use, personality traits and psychopathology in a Dutch twin sample (N = 9578, 66.8% female, 18–45 years). We also explored the nature of the association (underlying genetic factors, shared environmental factors or a causal relationship) with the co-twin control method.
Results: Lifetime ecstasy users (N = 945, 9.9%) were more often male, younger, living more often in urban areas, higher educated, less satisfied with life and more stressed than non-users. Ecstasy users scored differently on most personality and psychopathology scales compared to non-users and were more likely to have used every other substance we investigated. Whereas smoking tobacco and alcohol use often preceded first use of ecstasy, first ecstasy use often preceded first use of other illicit substances. A combination of scenarios (both causal and environmental/genetic) explained the strong associations between ecstasy and substance use.
Conclusions: Ecstasy users differ on many characteristics from non-users, and especially on illicit substance use. Our results indicate that causal effects may play a role in explaining the relationship between ecstasy use and other illicit substance use.

1. Introduction

One of the most popular illicit substances is ecstasy, or MDMA (3,4-methylenedioxymethamphetamine), with an annual prevalence of around 19 million users worldwide in 2014 (United-Nations-Office-on-Drugs-and-Crime, 2016). In Europe, approximately 1.7% of young adults (15–34 years) has taken ecstasy in 2014, with estimates ranging from 0.3% to 5.5% between countries (EMCDDA, 2016). Ecstasy is a recreational drug, popular in Western Europe and the United States; the prevalence of lifetime ecstasy use has been estimated to be ~11.3% in 12–34 year olds in the US (Palamar, Martins, Su, & Ompad, 2015), and ~13.0% in 15–34 year olds in the Netherlands (van Laar et al., 2016). Desired effects of ecstasy include an enhanced sense of well-being, emotional warmth, empathy, sensory motor perception and increased extraversion and a willingness to discuss emotionally-charged memories (NIDA, 2017). However, (occasional as well as regular) ecstasy use can also induce acute negative health effects such as hyperthermia, hypertension, elevated heart rate and hyponatraemia (Gowing, Henry-Edwards, Irvine, & Ali, 2002; de la Torre et al., 2000) and in some cases, ecstasy use can lead to death (Milroy, 2011). As ecstasy is still a popular drug of choice amongst young adults and is associated with some adverse health effects and intoxications, it is important to understand

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characteristics of ecstasy users in order to improve prevention.

Several studies have examined characteristics of ecstasy users before. What was found in these studies is that ecstasy is primarily taken by young adults, and more often by males than females (Degenhardt, Barker, & Topp, 2004; van Laar et al., 2016; von Sydow, Lieb, Pfister, Höfler, & Wittchen, 2002). In addition, users more often live in urbanized areas compared to non-users (Lai et al., 2016; van Laar et al., 2016). In a Dutch study, ecstasy was more often taken by higher educated than lower educated individuals (van Laar et al., 2016), but this was not true in an Australian study based on a household survey (Degenhardt et al., 2004). Recent ecstasy users are more likely to have used a range of other substances than non-ecstasy users (Smith, Farrell, Bunting, Houston, & Shevlin, 2011; Bobes et al., 2002; Degenhardt et al., 2004; Singer, Linares, Ntiri, Henry, & Minnes, 2004; Strote, Lee, & Wechsler, 2002). In addition, differences on personality characteristics have been observed; in particular, higher impulsivity, more sensation seeking, higher scores on extraversion, and higher levels of neuroticism and psychoticism are found in ecstasy users compared to non-users or non-ecstasy users (Bobes et al., 2002; Butler & Montgomery, 2004; ter Bogt, Engels, & Dubas, 2006; Singer et al., 2004). Several studies indicate that ecstasy users show more symptoms of psychopathology too, in particular depression and anxiety symptoms, compared with non-users (Guillot, 2007; Morgan, 2000). Whereas some studies reported that these symptoms already existed (long) before the use of ecstasy (e.g. (Huizink, Ferdinand, van der Ende, & Verhulst, 2006)), others suggested that ecstasy use may cause long-term psychopathology (Taurah, Chandler, & Sanders, 2014; Montoya, Sorrentino, Lukas, & Price, 2002). Studies investigating the relationship between ecstasy use and psychopathology other than depressive or anxiety symptoms, such as attention problems or antisocial behaviour, are scarce (Huizink et al., 2006).

Although characteristics of ecstasy users have been investigated in previous studies, many of these studies recruit people through targeted sampling, for example through advertising at dance parties, night clubs and raves (Degenhardt et al., 2004). The extent to which such specific samples are representative of ecstasy users in general is not clear. Moreover, many of these studies were based on small sample sizes and focus on a limited number of characteristics. Last, none of these studies corrected for (early) home environment and genetic factors when investigating the relationship between ecstasy use and other characteristics.

The aim of the present study is to identify characteristics of ecstasy users in a large (N = 9578) population-based sample of adults aged 18–45 years. First, we compare individuals who have used ecstasy during their lifetime (ecstasy users) with individuals who have never used ecstasy (non-users) on variables in the categories (1) demographics, health, wellbeing and stress, (2) substance use (licit and illicit), (3) personality traits and (4) symptoms of psychopathology. Subsequently, we investigate the order of substance use (age at initiation). Last, we aim to provide insight into the nature of the associations (causal, environmental, genetic) between ecstasy use and the variables described above using the co-twin control method.

2. Materials and methods

2.1. Study design and participants

Data were collected in the 10th survey (2013–2014) of a longitudinal study in Dutch twins and their family members register at The Netherlands Twin Register (Treur, Boomsma, Ligthart, Willemsen, & Vink, 2016; Willemsen et al., 2013). The study was approved by the medical ethical committee of the VU medical centre, Amsterdam, the Netherlands. In total, 19,699 individuals completed survey 10. We included participants who provided information on lifetime ecstasy use and were aged between 18 and 45 years because of the very low prevalence of ecstasy use (1.0%) among individuals older than 45 years. This resulted in a sample of 9578 individuals (66.8% females). Supplementary Table 1 shows the self-report questionnaires used for the current study.

2.2. Statistical analyses

We studied the association between lifetime ecstasy use and the variables described in Supplementary Table 1 using Generalized Estimating Equation (GEE) analysis. We added 'family' (indicating the family a person belonged to) as repeated subject factor to account for clustering within families. We conducted 4 separate sets of analyses with respectively (a) demographic variables, health, satisfaction with life and stress, (b) substance use variables, (c) personality variables, and (d) symptoms of psychopathology as predictors, and lifetime ecstasy use as outcome variable. First, univariate analyses were carried out. Variables that were significantly associated (after Bonferroni correction within group of variables) with lifetime ecstasy use were subsequently included in multivariate analyses. Age, age^2 and sex were included as covariates in all analyses. To avoid multicollinearity, age was standardised (before squaring it). The odds ratio is used to present the effect size of the individual variables. Participants with missing data were listwise excluded from the analyses. A logistic regression analysis was used to estimate the explained variance (with Nagelkerke pseudo R^2). To increase interpretation of comparability between associations of continuous variables and ecstasy use, we conducted secondary analyses in which we created z-scores of the continuous variables.

We determined the order of use for each substance compared to ecstasy use, by subtracting age at first ecstasy use from age at first use of another substance.

The associations between ecstasy use and the variables studied here might reflect several underlying mechanisms. Co-occurrence could be causal (where for example ecstasy use leads to use of other drugs or vice versa), or could be due to overlapping underlying factors such as genetic or environmental factors influencing both traits. The different explanations for co-occurrence are not mutually exclusive and are difficult to distinguish. We have explored the nature of the association with the co-twin control method (Stubbe, de Moor, Boomsma, & de Geus, 2007; Lichtenstein et al., 2002). For the co-twin control method, three groups were formed. Monozygotic (MZ) twin pairs discordant for lifetime ecstasy use (N = 103), same-sex dizygotic (DZ) twin pairs discordant for lifetime ecstasy use (N = 83) and 6206 unrelated twins by randomly selecting one person from each family. In this last group, 8.1% had ever used ecstasy. Within each group, the strength of the relationship between ecstasy use and the outcome variable is estimated. For the MZ and DZ twin pairs we used a paired *t*-test (for continuous variables) or McNemar test, a non-parametric test for 2 related samples (for dichotomous variables). In order to calculate the matched-pairs odds ratios we used the following formula: OR = b/c where b = the number of pairs where the ecstasy using twin is affected with regard to outcome measure (for example regular alcohol user, smoker) and the non-using twin is not and c = the number of pairs in which the non-using twin is affected and the using twin is not. The 95% confidence interval for the OR is calculated with: EXP(−1.96*SQRT((1/b)+(1/c))) and EXP(1.96*SQRT((1/b)+(1/c))) (IBM, 2019). A regression analysis was used for the group of unrelated subjects. We only explored the relationship for the variables that showed significant associations with ecstasy use in the GEE analyses.

Three possible scenarios for comparing the magnitudes of these relationships are shown in Fig. 1. *Scenario A*: if the influence is truly causal (i.e. exposure to ecstasy directly contributes to liability to the outcome) the ORs will be equivalent in all three groups: regardless of one's genetic and shared environmental status, exposure to ecstasy increases the risk for the outcome. *Scenario B*: If the association is not causal but is due to a third variable residing in shared family environment increasing both the risk to use ecstasy as well as liability for the outcome variable, one would expect the OR in the individual

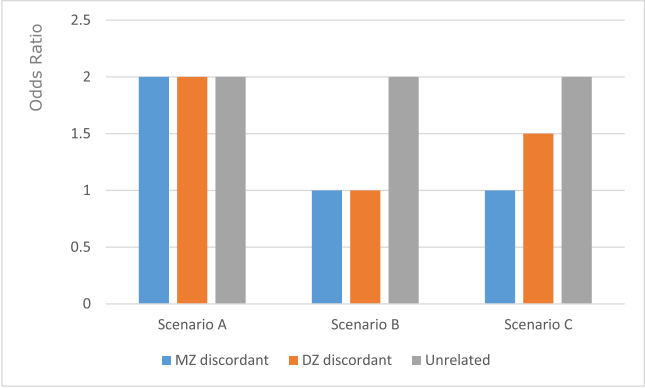

Fig. 1. The co-twin control method. The figure depicts a possible result pattern based on the Odds Ratio for the outcome variable given exposure to ecstasy in an unrelated sample, in members of dizygotic (DZ) same-sex twin pairs discordant for ecstasy use and in members of monozygotic (MZ) twin pairs discordant for ecstasy. Scenario A suggests a causal link between ecstasy and outcome. Scenario B suggests the relationship is due to the family environment that predispose to both ecstasy use and the other variable. Scenario C suggests the association is due to genetic factors that predispose to both ecstasy use and the outcome variable. The figure is intended to be heuristic, as opposed to involving precise point values corresponding with the exact heights of the lines in the figure.

sample to be larger and in the MZ and DZ discordant twin pairs equivalently lower. *Scenario C*: if the association is not causal but due to shared genetic influences that cause both ecstasy use and the outcome measure, one would expect the OR in the unrelated sample to be larger. In MZ discordant twin pairs the OR would be close to unity because the ecstasy using and non-using members of an MZ pair discordant for ecstasy use, would share their genetic predisposition for the outcome variable. In DZ discordant twins, the OR would be intermediate because the ecstasy using twin and the non-using co-twin share on average only 50% of their genetic predisposition to the outcome variable.

Power calculations for a matched pair design showed this sample size is sufficient to detect an OR of 1.9 or higher (http://sampsize.sourceforge.net/iface/s3.html, power 90%, 1:1 matched pair design) (G*power version 3.1.9.2, test: means: difference between two dependent means (matched pairs), alpha 0.05).

All statistical analyses were carried out using SPSS 24.0 and SPSS 25.0.

3. Results

3.1. Demographics, health, satisfaction with life and stress in relation to ecstasy use

Of the 9578 individuals in our sample, 945 (9.9%) indicated to have used ecstasy at least once in their life, of which 458 (51.3%) reported ecstasy use in the past year. The average age at onset of ecstasy use was 21.1 years (SD = 4.3). The percentage males was higher in the group of ecstasy users compared with non-users (Table 1). Ecstasy users were on average younger, lived in urbanized areas more often and were more often higher educated than non-users. Ecstasy users did not differ from non-users with regard to self-reported health and feelings of loneliness. However, ecstasy users did report more memory problems, less satisfaction with life, more stress at home and more financial stress compared to non-users. Urbanicity and financial stress explained most variance (R^2 = 1.9% and 1.7% respectively) followed by memory problems and sex (both R^2 = 0.8%). These variables, together with educational attainment remained significant in the multivariate analyses, while age, age^2, satisfaction with life and stress at home did not (Supplementary Table S2). The multivariate model explained 5.5% of the variance in lifetime ecstasy use. The co-twin control method (Supplementary Table 3) did not show clear patterns. ORs for all variables were rather low, so for most variables the power was insufficient to detect differences in our sample (see power calculation in methods). If any pattern was detectable, the pattern for memory problems and financial stress was mostly in line with scenario B (environment).

3.2. Lifetime ecstasy use and use of other substances

Ecstasy users were significantly more likely to have used every other substance compared to non-users (univariate analyses, Table 2). For example, ecstasy users were more often current smokers (33.9%) compared to non-users (11.6%) and had more often used cocaine (41% versus 1% respectively). Ecstasy users also had significantly higher mean scores on alcohol dependence as compared with non-users (9.30 versus 6.03). The explained variance was relatively high, ranging from 5.5–11.6% for smoking and alcohol, to 8.3–30.9% for illicit substances.

Multivariate analyses confirmed higher use of other substances in lifetime ecstasy users compared to non-users (Supplementary Table 2) although the ORs were somewhat lower. ORs were rather low for the licit substances (1.69 for regular drinking, 1.67 for ever smoking, non-significant for current smoking) indicating a limited risk to be a lifetime ecstasy user when being a smoker or a regular drinker. The ORs were higher for the illicit substances ranging from 4.44 for magic mushrooms to 11.93 for amphetamine. These results indicate a high risk of polydrug use for a lifetime ecstasy user. All substance use variables together (in combination with sex, age and age^2) explained ~53% of the variance in lifetime ecstasy use.

Licit substance use often preceded ecstasy use, with 83.5% of individuals started regular alcohol use and 73.2% regular smoking before ecstasy (Supplementary Table 4). Also, use of cannabis usually preceded first ecstasy use (84% of the sample). The majority of participants reported that ecstasy use preceded first use of other illicit substances (GHB, cocaine, ketamine use, magic mushrooms). In addition, ecstasy use either preceded (44.4%) or was initiated in the same year (48.0%) as amphetamine use.

With regard to licit substance use, the results of the co-twin control analyses for regular alcohol use and lifetime smoking were mostly in line with Scenario B (environmental factors), with low to moderate ORs (Table 3). For illicit substance use, the ORs were moderate to high and patterns were also in line with Scenario B (family environment) especially for ketamine and GHB (and to some extent for cocaine), while the pattern for cannabis was more in line with scenario C (genetic factors). For amphetamines and mushrooms the OR for DZ twin pairs could not be calculated because there were no twin pairs in which the non-using twin had the outcome while the using twin did not. In general, there was no evidence for a causal scenario where the ORs of the three groups were equal (Scenario A), but it must be noted that, especially for the illicit substances, the ORs in discordant MZ twins were high which in itself is already an indication for a causal pathway on top of possible other explanations.

3.3. Comparison of personality traits between ecstasy users and non-users

Lifetime ecstasy use was significantly associated with higher scores on neuroticism, extraversion, openness to experience and all scales of the Borderline personality scale and significantly lower scores on conscientiousness and agreeableness (Table 4). Self-harm and openness to experience explained most of the variance in lifetime ecstasy use (3.8% and 2.6% respectively).

Multivariate analyses confirmed that higher scores for extraversion, openness to experience, negative relationships, self-harm and lower scores for conscientiousness were related to a greater likelihood of lifetime ecstasy use also when corrected for other personality scores (Supplementary Table 2). Neuroticism, Agreeableness, Affect Instability and Identity problems were no longer associated with lifetime ecstasy

Table 1
Demographics, health, wellbeing and stress. Comparisons of lifetime ecstasy users and non-ecstasy users on demographics, health, wellbeing and stress using GEE, with lifetime ecstasy use as the outcome variables (univariate analyses, with age, age^2 and sex as covariates). N (number of participants for variable) can vary slightly per variable. OR and 95% Confidence Interval show the effect size, the p-value indicates significance of the comparison and the R^2 (=Nagelkerke Pseudo R^2) gives the explained variance for the individual variables.

	N	Lifetime ecstasy users	Non-ecstasy Users	OR [95%CI]	p-value	R^2
Sex, male N (%)	9576	396 (41.9%)	2779 (32.2%)	1.51 [1.32–1.73]	<**0.001**	0.8%
Age, mean (SD)	9578	27.34 (7.36)	28.79 (8.72)	0.98 [0.97–0.99]	<**0.001**	0.5%
Urbanicity, high N (%)	9396	488 (52.1%)	3067 (36.3%)	1.91 [1.65–2.21]	<**0.001**	1.9%
Educational level, high N (%)	9294	616 (67.4%)	5154 (61.5%)	1.28 [1.10–1.50]	**0.001**	0.3%
General health	9404	4.06 (0.70)	4.06 (0.69)	0.97 [0.88–1.07]	0.57	<0.1%
Memory problems, yes	9396	244 (26.4%)	1529 (18.0%)	1.54 [1.31–1.80]	<**0.001**	0.8%
Loneliness, high	9186	460 (51.5%)	4073 (49.1%)	1.11 [0.97–1.28]	0.12	<0.1%
Satisfaction with life	9346	26.26 (5.46)	26.88 (5.20)	0.98 [0.97–0.99]	<**0.001**	0.3%
Stress at home, moderate/high N (%)	9340	271 (29.6%)	2178 (25.9%)	1.27 [1.09 – 1.47]	**0.002**	0.1%
Stress at work, moderate/high N (%)	8768	335 (38.2%)	2721 (34.5%)	1.18 [1.03 – 1.36]	0.019	0.1%
Financial stress, moderate/high N (%)	9306	447 (49.0%)	2888 (34.4%)	1.79 [1.56 – 2.05]	<**0.001**	1.7%

Note: P-value threshold after Bonferroni correction: 0.05/12 = 0.004. P-values below this threshold are indicated in bold. Family ID was included as repeated subject factor to correct for family relatedness.

Table 2
Substance use. Comparisons of lifetime ecstasy users and non-ecstasy users on substance use using GEE, with lifetime ecstasy use as the outcome variables (univariate analyses, with age, age^2 and sex as covariates). N (number of participants for variable) can vary slightly per variable. OR and 95% Confidence Interval show the effect size, the p-value indicates significance of the comparison and the R^2 (=Nagelkerke Pseudo R^2) gives the explained variance for the individual variables.

	N	Lifetime ecstasy users	Non-users	OR [95%CI]	p-value	R^2
Alcohol dependence mean (SD)	4959	9.30 (5.07)	6.03 (3.92)	1.17 [1.15–1.19]	<**0.001**	10.6%
Regular alcohol use N(%)	9313	668 (71.6%)	3751 (44.8%)	2.73 [2.36–3.17]	<**0.001**	5.5%
Smoking cigarette, lifetime use N (%)	9560	837 (88.9%)	4470 (51.9%)	6.51 [5.31–7.97]	<**0.001**	11.6%
Current smoking, N (%)	9523	318 (33.9%)	998 (11.6%)	3.43 [2.95–4.00]	<**0.001**	6.1%
Cannabis, lifetime use N (%)	9565	818 (86.7%)	2257 (26.2%)	17.32 [14.21–21.11]	<**0.001**	28.0%
Cocaine, lifetime use N (%)	9533	381 (41.0%)	87 (1.0%)	58.17 [45.59–74.22]	<**0.001**	30.9%
Amphetamine, lifetime use N (%)	9527	300 (32.4%)	36 (0.4%)	84.49 [61.81–115.48]	<**0.001**	26.5%
Ketamine, lifetime use N (%)	9518	92 (9.9%)	9 (0.1%)	65.96 [37.74–115.28]	<**0.001**	8.3%
GHB, lifetime use N (%)	9504	121 (13.2%)	13 (0.2%)	70.42 [42.66–116.24]	<**0.001**	10.8%
Mushrooms, lifetime use N (%)	9509	278 (30.2%)	146 (1.7%)	20.34 [16.23–25.49]	<**0.001**	18.3%

Note: P-value threshold after Bonferroni correction: 0.05/11 = 0.005. P-values below this threshold are indicated in bold. Family ID was included as repeated subject factor to correct for family relatedness.

use when correcting for other personality traits. In the multivariate model, self-harm was the strongest predictor of lifetime ecstasy use. All personality traits together (in combination with sex, age and age^2) explained 9.5% of the variance in lifetime ecstasy use.

Concerning the results of the co-twin control method (Supplementary Table 3), no clear pattern was observed. The ORs were in general low. The ORs in the unrelated sample were more often significant, but this is due to the larger sample size.

3.4. Association between lifetime ecstasy use and symptoms of psychopathology

Ecstasy users reported significantly more symptoms of anxiety, depression, antisocial personality problems and ADH (attention deficit/hyperactivity) problems than non-users (Table 5). Ecstasy users and non-users did not differ on somatic problems and avoidant personality problems. The strongest association with lifetime ecstasy use were found with ADH problems (OR = 1.49, R^2 = 3.0%) and Antisocial personality (OR = 1.47, R^2 = 2.5%). In the multivariate analyses these two variables were the only variables that remained significant (Supplementary Table 2). The multivariate model explained 4.4% of the variance in lifetime ecstasy use.

The results of the co-twin control method (Supplementary Table 3) showed highest ORs in the unrelated sample, followed by somewhat lower ORs in DZ pairs and the lowest ORs in MZ pairs for Anxiety problems, Antisocial personality problems and ADH problems. This pattern is mostly in line with Scenario C (genetic factors), although scenario B (environmental factors) cannot be ruled out. Scenario B was more likely for depressive symptoms. However, power was limited in these models.

3.5. Secondary analyses

Repeating univariate analyses using z-scores of continuous variables as determinants and lifetime ecstasy use as outcome did not change the results (data not shown), except for ASR somatic Problem scale; whereas we did not find an association between ASR Somatic Problem scale and lifetime ecstasy use in our models, we show a significant relationship between the standardized scores and lifetime ecstasy use (OR = 1.10, R2 < 0.01), suggesting that lifetime ecstasy use is related to more somatic problems.

4. Discussion

In this large population-based sample aged 18–45 years, we found that ecstasy users differed from non-ecstasy users on basically all characteristics investigated (demographics, health, stress, substance use, personality, psychopathology) with the strongest differences in substance use. In our study, all substance use variables together with sex and age explained ~ 53% of the variance in lifetime ecstasy use. The association of lifetime ecstasy use was much stronger with illicit drug use than with licit substance use (smoking, drinking). Licit substance use preceded ecstasy use in most cases. Most individuals reported using ecstasy either before or in the same year as other illicit substances. As to the interpretation of this observed trend, it is important to note the difference between sequence and causation: a

Table 3
Co-twin control analyses for licit and illicit substance use variables that were significant in GLM analyses (Table 3). Comparison between ecstasy using twins and their co-twins separately for MZ and DZ twin pairs using McNemar test for dichotomous variables (for calculation OR, see method section) and paired *t*-test (in combination with regression analyses for OR) for the continuous variable alcohol dependence. Only twin pairs without missing data are included. In the last 5 columns a comparison of ecstasy users and non-users from an unrelated sample. Ecst users = ecstasy users, N = sample size (N pairs = number of twin pairs, N tot = total sample size, N ecst = sample size of ecstasy users), OR = Odds Ratio, p = p-value.

	Discordant MZ twin pairs					Discordant DZ twin pairs					Unrelated				
	N pairs	Ecst users% cases	Co-twins% cases	OR	P	N pairs	Ecst users% cases	Co-twins% cases	OR	P	N tot (N ecst)	Ecstasy users	Non-users	OR	P
Regular alcohol use	99	70.7%	65.7%	1.5 0.67–3.34	0.424	82	59.8%	47.6%	1.91 0.92–3.96	0.112	5463 (448)	72.5%	45.8%	3.2 (2,6–4,0)	< 0.001
Alcohol dependence score mean (SD)*	55	9.0 (4.1)	8.1 (4.6)	1.1 (1.0–1.2)	0.101	31	8.8	8.0 (5.5)	1.0 (0.9–3.2)	0.368	2922	9.3 (4.8)	6.0	1.2 (1.1–1.2)	< 0.001
Smoking cigarettes, lifetime use	103	80.6%	66,0%	3.5 1.41–8.67	0.007	83	85.5%	63.9%	3.3 1.47–7.18	0.004	5463 (451)	88.7%	55.5%	7.0 (5.2–9.4)	< 0.001
Current cigarette smoking,	101	23.8%	13.9%	3.5 1.15–10.63	< 0.001	81	23.5%	17.3%	1.6 0.67–3.59	< 0.001	5586 (450)	36.4%	12.6%	3.9 (3.2–4.9)	< 0.001
Cannabis, lifetime use	103	80.6%	54.4%	5.5 2.30–13.13	< 0.001	83	85.5%	49.4%	8.5 3.02–23.95	< 0.001	5610 (453)	86.1%	24.5%	16.4 (12.4–21.6)	< 0.001
Cocaine, lifetime use	102	35.3%	4.9%	32.0 4.37–234.19	< 0.001	80	35.0%	2.5%	14.0 3.34–58.77	< 0.001	5592 (446)	43.5%	1.1%	70.4 (49.9–99.5)	< 0.001
Amphetamine, lifetime use	103	23.3%	1.0%	11.5 2.71–48.78	< 0.001	81	25.9%	3.7%	na	< 0.001	5588 (445)	34.6%	0.5%	99.9 (63.3–157.6)	< 0.001
Ketamine, lifetime use	103	10.7%	1.0%	11.0 1.42–85.20	0.006	80	13.8%	1.3%	11.0 1.42–85.20	0.006	5579 (444)	10.4%	0.1%	183.7 (58.7–574.4)	< 0.001
GHB, lifetime use	103	16.8%	2.0%	16.0 2.12–120.65	< 0.001	78	17.9%	1.3%	14.0 1.84–106.47	0.001	5567 (439)	13.7%	0.1%	150.4 (60.9 – 371.6)	< 0.001
Mushrooms, lifetime use	100	25.0%	2.0%	12.5 2.96–52.77	< 0.001	78	25.3%	1.3%	na	< 0.001	5577 (442)	31.7%	1.5%	26.7 (19.5–36.5)	< 0.001

*Only available if both twins of a twin pair drank regularly in the past year.

Table 4
Personality. Comparisons of lifetime ecstasy users and non-ecstasy users on the big five personality traits measured with the NEO, and on the subscales of Personality Assessment Inventory – Borderline (PAI-BOR) using GEE, with lifetime ecstasy use as the outcome variables (univariate analyses, with age, age^2 and sex as covariates). N (number of participants for variable) can vary slightly per variable. OR and 95% Confidence Interval show the effect size, the p-value indicates significance of the comparison and the R^2 (=Nagelkerke Pseudo R^2) gives the explained variance for the individual variables.

	N	Lifetime ecstasy users Mean (SD)	Non-users Mean (SD)	OR[95%CI]	p-value	R^2
NEO - Neuroticism	9396	19.91 (8.43)	18.98 (8.27)	1.02 [1.01 – 1.03]	<**0.001**	0.2%
NEO - Extraversion	9396	31.54 (6.15)	30.15 (6.20)	1.03 [1.02 – 1.05]	<**0.001**	0.9%
NEO - Conscientiousness	9396	31.87 (6.55)	33.86 (5.93)	0.95 [0.94 – 0.96]	<**0.001**	2.0%
NEO - Openness to experience	9396	28.89 (6.71)	26.51 (6.21)	1.06 [1.04 – 1.07]	<**0.001**	2.6%
NEO - Agreeableness	9396	31.16 (5.81)	32.31 (5.40)	0.97 [0.96 – 0.99]	<**0.001**	0.8%
PAI BOR - Affect instability	9549	5.12 (3.32)[1]	4.40 (3.01)[1]	1.35 [1.23 – 1.47]	<**0.001**	0.9%
PAI BOR – Identity Problems	9551	4.75 (3.21)[1]	4.15 (2.95)[1]	1.32 [1.20 – 1.44]	<**0.001**	0.7%
PAI BOR – Negative relationships	9542	5.37 (3.25)[1]	4.52 (2.89)[1]	1.47 [1.33 – 1.62]	<**0.001**	1.4%
PAI Bor - Self Harm	9546	3.28 (2.89)[1]	2.12 (2.15)[1]	1.67 [1.53 – 1.82]	<**0.001**	3.8%
PAI Bor – Total Score	9552	18.51 (9.78)[1]	15.19 (8.43)[1]	1.43 [1.34 – 1.53]	<**0.001**	2.6%

Note: P-value threshold after Bonferroni correction: 0.05/10 = 0.005. P-values below this threshold are indicated in bold. Family ID was included as repeated subject factor to correct for family relatedness.[1]Mean and SD of the raw scores for the variable are presented.

particular order of events does not always imply causation. Other mechanisms could also underlie the association between ecstasy use and subsequent other illicit drug use (see below).

Within the first set of variables (demographics, health, wellbeing and stress) urbanisation and financial stress showed the strongest association with lifetime ecstasy use, followed by memory problems and being male. Our finding that ecstasy users, compared to non-users, more often lived in urban areas is in line with previous studies in the Netherlands (van Laar et al., 2016), Australia (Lai et al., 2016) and the United states (Gfroerer, Larson, & Colliver, 2007; Wu, Schlenger, & Galvin, 2006). Gfroerer et al. stated that substance (ab)use in general is not specifically an urban problem (Gfroerer et al., 2007), but for ecstasy use this seems to be an important characteristic. This may be due to a higher availability of ecstasy in urban areas, but also to a higher frequency of recreational settings where ecstasy is used in urban areas, such as clubs, nightlife events and dance festivals (Bryant et al., 2016; Banta-Green et al., 2009; Lai et al., 2013; Warren, Smalley, & Barefoot, 2015). As far as we know, no other studies explored the relationship between financial stress and ecstasy use. Ayllon and Ferreira-Batista suggested that the consumption of certain drugs was positively related to increasing unemployment rates (due to the Great Recession). The mechanism for this phenomenon could be the 'economic stress' mechanism where people deal with uncertainty about future income by taking substances as a form of self-medication (Ayllón & Ferreira-Batista, 2017). This is in line with our results from the co-twin control analyses, where scenario B was the most likely scenario: a non-causal association between ecstasy and financial stress due to the (family) environment. Unemployment or other stress about (family) income could be such an environmental factor. Memory deficits are a well-known side effect of (regular) ecstasy use (Laws & Kokkalis, 2007) although with cross-sectional designs it cannot be determined whether memory problems were caused by ecstasy use or already existed before first-time use. We did not find evidence for a causal relationship between ecstasy use and memory problems with the co-twin control study, but power was limited. If any pattern could be detected it was in line with scenario B (overlapping environmental influences causing the association between ecstasy use and memory problems).

Significantly higher prevalence rates were observed for ecstasy users than their non-using co-twins for illicit substances (cannabis, cocaine, amphetamine, ketamine, GHB and magic mushrooms), but not for smoking and alcohol use. This suggests that either ecstasy use itself is associated with use of other illicit substances (for example positive experience with ecstasy leads to use of other drugs), or that an environmental factor not shared by the twin pairs (for example visiting dance events or having substance using friends) influences the risk to use of both ecstasy and other illicit substances. The results of the co-twin control analyses showed that the association between ecstasy and licit or illicit substance use is partly explained by a third factor, which represents shared environmental factors and/or genetic factors. For most substances, it was more likely that this third factor represented shared environmental factors, while for cannabis a genetic factor was more likely. However, for the illicit substances the ORs in discordant MZ twin pairs were high, which means that the ecstasy using twin has a significantly higher risk to use illicit substances compared to the non-using co-twin. This is a strong indication for a causal relationship between ecstasy and other illicit drug use (since genetic and shared family environmental factors are the same in MZ twin pairs). A causal effect means that ecstasy use itself is increasing the risk to use of other drugs, for example through positive experiences after ecstasy use. Based on our results it is likely that there is a causal relationship on top of environmental (or genetic factors) that play a role in explaining the association between ecstasy and other illicit drug use.

Table 5
Psychopathology. Comparisons of lifetime ecstasy users and non-ecstasy users on the Adult Self Report using GEE, with lifetime ecstasy use as the outcome variables (univariate analyses, with age, age^2 and sex as covariates). N (number of participants for variable) can vary slightly per variable. OR and 95% Confidence Interval show the effect size, the p-value indicates significance of the comparison and the R^2 change (=Nagelkerke Pseudo R^2) gives the explained variance for the individual variables.

	N	Lifetime ecstasy users	Non-users	p-value	OR [95% CI]	R^2
ASR Anxiety problems, M (SD)	9107	3.23 (2.85)[1]	3.02 (2.61)[1]	**0.002**	1.14 [1.05 – 1.23]	0.1%
ASR Depressive problems, M(SD)	9115	4.65 (4.42)[1]	4.03 (3.95)[1]	<**0.001**	1.20 [1.12 – 1.28]	0.4%
ASR Somatic problems, M(SD)	9080	2.03 (2.40)[1]	1.93 (2.22)[1]	0.11	1.07 [0.99 – 1.16]	<0.1%
ASR Avoidant personality problems, M(SD)	9109	2.38 (2.47)[1]	2.55 (2.43)[1]	0.12	0.94 [0.87–1.02]	0.1%
ASR Antisocial personality problems, M(SD)	9117	3.30 (3.27)[1]	2.27 (2.21)[1]	<**0.001**	1.47 [1.34 – 1.62]	2.5%
ASR ADH problems, M(SD)	9115	6.17 (4.49)[1]	4.49 (3.70)[1]	<**0.001**	1.49 [1.38–1.61]	3.0%

P-value threshold after Bonferroni correction: 0.05/6 = 0.008. P-values below this threshold are indicated in bold. Family ID was included as repeated subject factor to correct for family relatedness. [1]Mean and SD of the raw scores for the variable are presented.

We showed that ecstasy users have different personality scores on all subscales compared to non-users. This is in line with previous, smaller studies that reported associations in the same directions for comparable traits (Bobes et al., 2002; Butler & Montgomery, 2004; Singer et al., 2004; ter Bogt et al., 2006). The power in our co-twin control analyses was not sufficient for most personality scores to further clarify the nature of the relationship.

In the present study, ecstasy users showed significantly less favourable scores on most psychopathology scores compared to non-users. Previous, relatively small studies showed contrasting results, with some studies suggesting ecstasy as causal factor for psychopathology, like depression and anxiety (Taurah et al., 2014), while others excluded this causality (Durdle, Lundahl, Johanson, & Tancer, 2008; Falck, Wang, & Carlson, 2008). A longitudinal study (N = 1580) suggested that childhood depression and anxiety could predict ecstasy use in adolescence or young adulthood (Huizink et al., 2006), but this association could still be due to a third factor (genetic or environmental). Based on our co-twin control study (although power was limited), we did not find evidence for a causal pathway. For Anxiety problems, Antisocial personality problems and ADH problems Scenario C (underlying genetic factors) was more likely, although Scenario B (shared environmental factors) could not be ruled out. Scenario B was more likely for depressive symptoms.

Indeed, from previous twin studies we know that genetic factors play a role in personality and psychopathology (Bassir Nia et al., 2018; Briley & Tucker-Drob, 2014) and we recently showed for the first time that genetic factors (in addition to environmental factors) play a role in ecstasy use, with a heritability estimate of 74% (Verweij et al., 2017). Future research with a larger number of twin pairs should investigate whether and which specific genetic or environmental factors for ecstasy use and psychopathology overlap in order to explain their co-morbidity.

The current study has several limitations. Lifetime ecstasy use (yes/no) was used without distinguishing experimenters from regular users. It is possible that characteristics such as psychopathology, but also other drug use, differ between incidental and regular ecstasy users. Another issue that needs consideration is polydrug use: most ecstasy users also use other substances and the use of other substances is also associated with psychopathology and personality traits. Also, we did not have longitudinal data on ecstasy use; it is possible that current non-users will start using ecstasy in a later phase of their life. Furthermore, we used self-report data which may have led to underreporting of undesirable behaviour such as substance use. However, bias is likely to be limited in this sample (Vink et al., 2004). Lastly, the power of the co-twin control study to detect significant differences was not sufficient for several variables (when OR < 1.9 (i.e. for demographics, health, alcohol dependence, psychopathology and personality), see Supplementary Table 3), and no firm conclusions can be drawn for these variables with regard to the underlying mechanism explaining the nature of the associations.

In conclusion, we aimed to provide a broad overview of characteristics of ecstasy users compared to non-users in a large, population-based sample. Our data clearly demonstrate that ecstasy users in a population-based sample differed from non-ecstasy users on a wide range of variables including substance use, urbanicity, financial stress, personality and psychopathology. Use of licit substances often preceded first use of ecstasy, and first ecstasy use often preceded first use of other illicit substances. These findings, combined with those from the co-twin control analyses, suggest ecstasy is highly associated with the use of other illicit substances, often as starting substance of choice. The association may be due to several factors, most likely environmental variables (e.g. accessibility to the substance or recreational setting where the drug is used), but genetic factors cannot be ruled out. In addition, causal effects play a role in explaining the relationship between ecstasy use and other illicit substance use. No evidence was found for a direct causal relationship underlying the link between ecstasy use and personality, psychopathology or demographics and well-being in the current study, but power was limited. Last, the fact that ecstasy use is related to multiple factors with modest to large effects underscores the need for prevention and intervention strategies to focus on a broad range of factors.

CRediT authorship contribution statement

Annabel Vreeker: Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Tibor M. Brunt:** Conceptualization, Methodology, Writing - original draft. **Jorien L. Treur:** Investigation, Conceptualization, Writing - review & editing. **Gonneke Willemsen:** Writing - review & editing. **Dorret I. Boomsma:** Supervision, Methodology, Writing - review & editing. **Karin J.H. Verweij:** Methodology, Writing - review & editing. **Jacqueline M. Vink:** Supervision, Investigation, Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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